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Evaluation of serum fucose and fucose related parameters in beta- thalassemia major

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Abstract

Background and objective: Beta-thalassemia syndrome is characterized by either absent or lower-than-normal production of the beta-globin chain in hemoglobin, which can cause various health problems. α- L-fucose is a methyl pentose sugar, which is a part of the glycan's of a significant category of compounds referred to as glycoconjugates; glycoproteins and glycolipids. The major aim of the current study is to evaluate using serum fucose parameters as biomarkers or indicators for beta- thalassemia disease.

Methods: The current study was materialized on 45 Beta-thalassemia major patients and 45 healthy volunteer individuals. Blood sample collections were performed at Thalassemia Center (Akre and Erbil). Serum Fucose and related parameters total fucose (TF), protein bound fucose (PBF), protein bound hexose (PBH), lipid associated fucose (LAF), and free fucose (FF) were measured using UV/VIS spectrophotometry.

Results: Beta-thalassemia major (BTM) patients had a significantly higher serum levels of TF and FF compared to the controls. A significant reduction in serum PBF was observed in patients. However, differences in PBH and LAF were not statistically significant. The PBH mean and standard deviation in patients were 6.421 and 3.085, respectively, compared to 6.817 and 3.758 in controls (P = 0.5858). For LAF, patient values were 3.281 and 2.225, versus 2.452 and 1.960 in controls (P = 0.0640).

Conclusion: The results inferred significant increase in serum TF and FF, and a significant decrease in serum (PBF) in Beta-thalassemia major patients. The results suggest that TF, FF and PBF parameters can be used as diagnostic markers for the disease.

Keywords: α-L-fucose, Fucose parameters, Beta-thalassemia major.

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Introduction

Beta-thalassemia (BT) syndrome is characterized by either absent or lower-than-normal production of the beta-globin chain in hemoglobin, which can cause various health problems. The most severe kind, beta-thalassemia major, typically first appears in early childhood and results in severe anemia that requires regular blood transfusions for the remainder of one's life. It is crucial to comprehend these conditions to manage and treat them successfully (1, 2). Beta-thalassemia BT is a set of inherited diseases caused by mutations in the beta-globin gene which located on chromosome 11 that lead to insufficient hemoglobin production (2, 3). Around the world, thousands of people have β-thalassemia BT, a hereditary condition. It is distinguished by abnormalities in the production of hemoglobin (Hb) beta chains, which result in a variety of phenotypes, ranging from asymptomatic to severely anemic. This disease comes in three forms: Major (BTM), intermediate (BTI), and minor (BTMi) beta-thalassemia. BTM patient usually show significant anemia and require regular blood transfusions throughout the first two years of life. Unlike BTi patients who have substantial anemia and might not need regular blood transfusions, BTMi phenotypic patients are clinically asymptomatic and could have mild anemia (1, 4). True illness burden linked with hereditary haemoglobinopathies is unclear, despite the fact that they are the most common monogenic disorders. At least 3.4% of the under-five mortality rate is attributable to the 300,000 to 500,000 infants each year born with a severe haemoglobin issue. More than seven percent of the global population may have a hemoglobin variation (1, 5).

The term "glycome" refers to the complete family of glycoconjugates, which are made up of carbohydrate chains or glycan’s that are covalently attached to protein or lipid molecules. The process that creates glycoconjugates, which vary in length, glycan sequences, and linkages, is called glycosylation. The dynamic process of glycoconjugates synthesis is influenced by the local environment, which includes sugar precursors, enzymes, and the structures of organelles, as well as the kinds of cells and signals from cells (6, 7). A monosaccharide called alpha-L-fucose is essential for immunological responses and glycosylation, among other biological functions. It is frequently present in human, insect, and microbial glycan’s and is essential to the construction of glycolipids and glycoproteins (6). Alpha-L-fucose participates in the process of fucosylation, a posttranslational modification that modifies the behavior and function of proteins, hence impacting immunological responses and cellular interactions (8, 9). Neuroinflamation, Exogenous L fucose has been shown in studies to reduce

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neuroinflammation by promoting core fucosylation, which controls inflammatory signaling pathways (10). Enzymes known as α-L fucosidases catalyse the removal of fucose residues from glycoproteins, with various microbial sources exhibiting diverse substrate specificities (11). For instance, a robust α-L fucosidase from Prevotella nigrescens has shown high efficiency in glycoengineering therapeutic antibodies (3, 12).

Fucosylation is a significant post-translational modification process that uses fucosyl transferases to add fucose residues to proteins, glycolipids, and glycan's. This process affects a wide range of cellular connections and activities (13, 14). In cancer biology, aberrant fucosylation plays a major role in cell invasion, immunesurveillance, metastasis, and proliferation. It is controlled by elements such as aberrant enzyme expression and substrate availability (15). When it comes to beta thalassemia major and oxidative stress, glycoconjugates are essential (15).

Methods

Ethical Approval: This study was approved by the Ethics Committee of the College of Health Sciences, Hawler Medical University. Verbal informed consent was obtained from all participants prior to inclusion. Ethic form number (Sc.E.C.11J1)

Study population: This study was conducted between October 2024 and June 2025. Sample collections were performed at Thalassemia center in (Akre and Erbil). The testing was analyzed at the research center of Hawler Medical University. This study was enrolled (90) Samples, included 45 male patients with major β-Thalassemia (patient group) with age range of 10-25 years. The study also included (45) male healthy individual (control group), with the same age range (10-25 years). Inclusion criteria, were individuals aged 10–25 years, male only, including patients with a confirmed diagnosis of beta-thalassemia major (based on genetic or clinical criteria) who were on regular blood transfusion therapy, as well as healthy controls without beta-thalassemia or other systemic diseases. And the exclusion criteria included individuals with other blood disorders (e.g., sickle cell anemia), chronic inflammatory or infectious diseases (e.g., rheumatoid arthritis), those taking antioxidant supplements, and those with significant liver, kidney, or heart dysfunction.

Sample collection: Before obtaining the samples, individuals were directed to fill the questionary to avoid exclusion criteria. Approximately 5ml to 7 ml fasting blood obtained from participant who instructed to attend the laboratory in the morning. After that, blood samples were placed in a container without an anticoagulant (Gel tube) and allowed to sit at room temperature for 10 to 15 minutes. The serum was then

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separated using a centrifuge set to 3000 rpm for approximately 10 minutes. The sera was divided into a number of clean plain tubes, which stored at (- 20C°). The serum that was separated is being used for the measurement of serum fucose and associated parameters.

Principles of parameters:

1- Serum TF was measured utilizing the Dishes and Shettels method (16). The technique depends on the direct interaction between concentrated sulphuricacid (H_2SO_4) and the components of the sample. Then the reactant was combined with cysteine and the resulting colorimetric products were measured at 396 nm and 430 nm (16, 17).

2- Serum (PBF) was determined using Dische and Shettels technique (16). Serum proteins were precipitated using ethanol. The precipitated protein was resuspended in NaOH to make it soluble once more. A chromatic product was generated when fucose (in solution) reacted with a color developer (cysteine hydrochloride) in a strongly acidic media. The color intensity was quantified at 396 nm and 430 nm (16, 18, 19).

3- Serum LAF was estimated depending on Katopodis method. The entire amount of serum lipid was extracted using a 2:1 mixture of methanol and v/v chloroform. Then, the Dische & Shettles method was used to quantify the amount of fucose after the protein is precipitated by a phosphotungestic acid solution (16, 18).

4- The level of serum PBHex was assessed based on the interaction with Orcinol (16, 18). At room temperature, 95% ethanol was used to precipitate the protein-carbohydrate complex's hexose components, which were then measured using the Orcinol reaction. Next, the absorbance was quantified at 520 nm using spectrophotometric apparatus.

5- Serum FF was determined (16, 18) using the following equation:

Free Fucose (FF) = Total Fucose - (LAF+ PBF)

Statistical Analysis: Statistical analysis was performed using GraphPad Prism v9. Normality was tested with the Shapiro-Wilk test. Parametric data were analyzed using an unpaired t-test (mean ± SD), while non-parametric data were assessed using the Mann-Whitney U test (min, 25th, median, 75th, max). A P-value <0.05 was considered significant.

Results

Table 1 show the mean and standard deviation (±SD) of serum total fucose (TF), free fucose (FF), lipid associated fucose (LAF), and protein bound hexose (PBH) in beta-thalassemia patients and control groups. The results of serum TF and FF indicated that there was a significant increase (P <0.001) in its level in beta-thalassemia patients and control groups. On the other hand, the

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average serum level of TF and FF in Beta-thalassemia BT patients was double than those of healthy individuals. While the results of (LAF and PBH) showed that there was a non-significant difference in serum (LAF and PBH) Levels in beta-thalassemia patients and control groups.

Table 2 provides the minimum, 25% percentile. Midian, 75% percentile and Maximum of serum protein bound fucose (PBF) of Beta-thalassemia patient and control groups. Normality test was done for the results, which indicated that the data of PBF was non-parametric. So (the minimum, 25% percentile. Midian, 75% percentile and Maximum of serum protein bound fucose (PBF) were calculated). The result of serum PBFs level showed that there was a statistically significant decrease (P <0.001) in PBF parameters in Beta-thalassemia group when compared with control group.

Table 1. The mean±standard deviation (Mean±SD) of serum fucose parameters, PBH, LAF, FF (except PBF level) in Beta-thalassemia patients and Control group

Biochemical parameters (mg/dL)	Beta-thalassemia major group (N=45) Mean ± SD	Controls group (N=45) Mean ± SD	P-value
Serum (TF)	145.6±37.33	127.3±26.90	0.0092**
Serum (PBH)	6.421± 3.085	6.817±3.758	0.5858 NS
Serum (LAF)	3.281± 2.225	2.452±1.960	0.0640 NS
Serum (FF)	136.9± 41.63	117.8 ±26.49	0.0111*

* By unpaired t test for parametric sample.

Table 2. The minimum, 25% percentile. Midian, 75% percentile and Maximum of serum protein bound fucose (PBF) levels of Beta-thalassemia patient and control groups

Biochemical Parameters (PBF) (mg/dL)	Beta-thalassemia patients (N=45)	Controls group (N=45)
Minimum	0.02449	0.1224
25% Percentile	0.18371.837	
Median	2.0573.576	
75% Percentile	10.8113.05	
Maximum	19.69	21.21

*By Man-Whitney test for non- parametric sample. P. Value = *

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Table 3 show statistically significant negative correlation was observed between total fucose levels and PBF (r = -0.4230, P = 0.0038). In contrast, PBH exhibited a significant positive association with total fucose (r = 0.3445, P = 0.0205). Although a negative correlation was also noted between total fucose and LAF, it did not reach statistical significance (r = -0.2692, P = 0.0737). Additionally, free fucose demonstrated a remarkably strong positive correlation with total fucose (r = 0.9890, P <0.0001).

This study used males since hormonal changes in females during menstruation, pregnancy, and lactation may affect serum glycoproteins. The age range (10-25) years included in this study, because during this period, patients with beta-thalassemia major usually receive iron chelation therapy and frequent blood transfusions. A diverse group of hereditary hemoglobinopathies known as beta-thalassemia are brought on by genetic mutations in the beta-globin gene that interfere with the production and synthesis of beta-globin chains in hemoglobin (20). Iron excess, persistent hemolytic anemia, and inadequate erythropoiesis are the hallmarks of the illness. Clinical signs include asymptomatic carriers and severe anemia that necessitates continuous, lifelong blood transfusions and the ensuing debilitating effects. The treatment of individuals with severe β-thalassemia is a global health issue, especially in developing nations. Until recently, iron chelation therapy and regular transfusions were the exclusive care choices, with only a limited number of patients eligible for allogeneic hematopoietic stem cell transplantations (20).

Table 3. Show the correlation between Total fucose (TF) with Protein Bound Fucose (PBF), protein bound hexose (PBH), lipid associated fucose (LAF), and free fucose (FF)

Total Fucose Parameters	r	P-Value
PBF	-0.4230	0.0038 **
PBH	0.3445	0.0205 *
LAF	-0.2692	0.0737
Free Fucose	0.9890	<0.0001 ****

P-values are indicated by asterisks to denote levels of statistical significance: P <0.01 (**) and P <0.0001 (***).

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The result of the present study showed that Serum TF was significantly elevated in Beta-thalassemia BT patient when compared to the healthy groups. The elevation in this parameter may be caused by several reasons; one of the primary reasons is the chronic hemolysis and ineffective erythropoiesis characteristic of beta-thalassemia, which lead to continuous turnover and breakdown of erythrocytes. This process increases the release of glycoproteins and glycolipids into the circulation. The second reason, is due to the elevated oxidative stress observed in thalassemia patients that can alter glycosylation pathways, leading to increased synthesis and release of fucosylated compounds (21). Moreover, liver dysfunction, commonly associated with iron overload in these patients, thus it may impair the clearance of fucosylated proteins, further contributing to their accumulation in serum. Finally the significant elevation of serum total fucose (TF) levels in β-thalassemia patients may be ascribed to increased apoptosis and degradation of red blood cells (RBCs), leading to the release of fucose-rich glycoconjugates into the bloodstream. Khalid (2019) study supported this idea, indicating that high levels of fucose can aggravate apoptosis, contributing to early RBC degradation in β-thalassemia (22). The result of serum total fucose (TF) levels in this study was in agreement with the study of Al-Hakeem (2013) who stated that total fucose level increased in Beta-thalassemia patient compared to control Group (23).

The Results showed that serum (PBF) levels dropped markedly in Beta-thalassemia major patients in comparison with the control group. The decreased serum protein-bound fucose (PBF) levels in beta-thalassemia patients are likely due to a combination of ineffective erythropoiesis and increased destruction of (RBCs). This heightened turnover can lead to alterations in glycosylation patterns of serum proteins, including reduced fucosylation, liver dysfunction affecting glycoprotein synthesis, and oxidative stress altering metabolic pathways. Destruction of unstable haemoglobin and iron overload, both encourage the production of excess free radical molecules, are the main sources of oxidative stress in thalassemia. Oxidative stress exacerbates symptoms such as heightened hemolysis, inefficient erythropoiesis, and functional impairment of essential organ, including the heart and liver (24). These factors collectively contribute to the observed reductions in PBF concentrations in Beta-thalassemia patients compared to the control group. This is consistent with study conducted by Doltchinkova (2023) who investigated the alterations in the erythrocyte membranes of beta-thalassemia patients, specifically noting that β-thalassemia erythrocytes exhibit a decrease in glycoproteins and sialic

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acids (25). The findings suggest that such changes may contribute to the pathophysiology of beta-thalassemia by affecting red blood cell stability and lifespan. The result of this study was disagreed with a study done by Assi (2019) that showed a notable increase in the amounts of protein bound fucose (PBF) in thalassemic patients in comparison with healthy group (26). This was due to the clinical severity and problem or complications of the disease. A study done by Ali (2012) was reported that the level of protein bound fucose (PBF) is significantly higher in patient with myocardial infraction (MI) when compared to control groups (19). They mentioned that the increase was due to myocardial tissue destruction.

In case of serum PBH levels, the results demonstrated that there was a non-significant decrease in serum PBH in Beta-thalassemia patients when compared to the healthy group. The reduction in the mean serum protein Bound Hexose (PBH) levels may be ascribed to modified glycosylation processes and elevated oxidative stress in thalassemic individuals, which may prevent protein glycation and diminish circulating glycoprotein levels. Moreover, prolonged haemolysis and hepatic impairment in these patients may influence the synthesis and stability of serum glycoproteins (24, 27, 28).

While the result of Serum (LAF) levels indicated that non- significant alterations were seen in Beta-thalassemia patients compared to the healthy groups. The increase in the mean of serum LAF levels in Beta-thalassemia (BTM) patients in this study, relative to the control group, may be ascribed to heightened oxidative stress, Ineffective erythropoiesis and regular blood transfusions define Beta-thalassemia major, both of which cause iron excess. Iron accumulation helps to generate reactive oxygen species (ROS) molecules, which causes oxidative stress (21). The present study also indicated that Serum (FF) level in Beta-Thalassemia patients significantly increased. This elevation may be attributed to increased red blood cell turnover and apoptosis. Insufficient erythropoiesis and increased red blood cell (RBC) breakdown characterize B-thalassemia (29). This process leads to the release of fucose-rich glycoconjugates into the bloodstream, thereby elevating serum fucose levels.

The observed significant negative relationship between total fucose and PBF ($r = -0.4230$, $P = 0.0038$) may indicate disruptions in glycosylation pathways, potentially arising from ineffective erythropoiesis commonly seen in Beta Thalassemia Major. This is in line with evidence suggesting that fucosylation processes are influenced by hematopoietic activity and inflammatory responses (30). Conversely, the positive association between total fucose and PBH

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(r = 0.3445, P = 0.0205) may reflect an adaptive response aimed at enhancing hemoglobin synthesis as a compensatory mechanism for chronic anemia (32). While the negative correlation between total fucose and LAF did not reach statistical significance, the downward trend may still hint at a connection between fucose metabolism and hepatic function, which has been noted in previous studies involving thalassemia patients (31). Furthermore, the exceptionally strong correlation between free and total fucose (r = 0.9890, P <0.0001) underscores a tight metabolic link, supporting the idea that circulating free fucose levels serve as a reliable indicator of systemic fucosylation status in serum (30).

Conclusion

The research referred to drawing the following findings from this study: significant increase in serum (TF and FF) and significant decrease in serum (PBF) in beta-thalassemia major patients. The results suggest that these parameters (TF, FF, and PBF) can be used as a diagnostic marker for the disease.

Competing interest

The authors declare that they have no competing interests.

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